REMARKS

Upon entry of this amendment, claims 56, 59, 60, 67-69 and 105-108 are under examination. Applicants have canceled claims 1-55, 57, 58, 61-66 and 78-104, herein, for being drawn to non-elected subject matter. Applicants reserve the right to pursue the subject matter of these claims in a divisional application. Applicants have amended claims 56 and 105, herein. Support for these amendments can be found, for example, on page 40, lines 11-12 of the instant specification and in claim 58 as filed. The Examiner has withdrawn claims 70-77 for being drawn to non-elected species. Applicants submit that claim 56 is a linking claim for the species of the invention and is being examined with the elected invention. When all claims directed to the elected invention are allowable, should any linking claim be allowable, the restriction requirement between the linked inventions must be withdrawn. Any claim(s) directed to the non-elected inventions, previously withdrawn from consideration, which depends from or requires all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability.

Applicants have also amended the specification to correct the priority claim and to correct reference to trademarks in the specification. Applicants have also amended the title as suggested by the Examiner to be more descriptive. No new matter has been added.

Objections to the Specification

Priority

The Examiner objected to the priority claim, on page 2 of the Office Action, because of the improper use of the phrase "continuation-in-part" in a claim of foreign priority. Applicants have amended the priority claim and submit that this objection is overcome. Applicants have requested certified copies of these applications and will supply them to the Examiner as soon as they receive them.

Trademarks

Applicants have amended the specification to correct the recitation of trademarks, as suggested by the Examiner.

Title

The Examiner has objected to the title of the instant application, on page 3 of the Office Action, for not being sufficiently descriptive and requests that Applicants amend the title to include reference to CD69. Applicants have amended the title according to the Examiner's suggestions and submit that this objection is overcome.

Claim Rejections

Rejections under 35 U.S.C. § 112, Second Paragraph.

The Examiner has rejected claims 56-60, 67-69 and 105-108 on pages 3-4 of the Office Action, under 35 U.S.C. § 112, second paragraph, for indefiniteness. Applicants have canceled claims 57 and 58, so this rejection is moot as it regards these claims. The Examiner asserted that the recitation of "depleting anti-CD69 antibody" is indefinite because CD69 is merely a laboratory term and does not clearly identify the antibody because artisans could use this same designation for a distinct biological material. The Examiner suggested that Applicants claims the antibody in terms of the sequence that it binds to.

Applicants have amended claim 58 to specify that he CD69 antibody must specifically bind SEQ ID NO:2. Applicants submit that claims 56, 59, 60, 67-69 and 105-108 are definite and respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph.

The Examiner has rejected claims 56-60, 67-69 and 105-108 on pages 4-6 of the Office Action, under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants have canceled claims 57 and 58, so this rejection is moot as it regards these claims. The Examiner asserted that because the instant specification teaches that human CD69 refers to a polypeptide that is at least about 85% homologous to SEQ ID NO:2, that the claims could possibly encompass antibodies that specifically bound to variants of SEQ ID NO:2, but that could not specifically bind SEQ ID NO:2, itself.

Applicants have amended claim 58 to specify that he CD69 antibody must specifically bind SEQ ID NO:2. Thus, the claims do not encompass antibodies that would bind to a variant of SEQ ID NO:2 and not SEQ ID NO:2, itself. Applicants submit that claims 56, 59, 60, 67-69 and 105-108 are enabled and respectfully request that this rejection be withdrawn

Rejections under 35 U.S.C. § 103.

The Examiner has rejected claims 56-60, 67-69 and 105-108, on pages 6-7 of the Office Action, for obviousness over McInnes *et al.* Immunol. Today 19(2):75-9 (Feb. 1998) ("McInnes #1") in light of Ledbetter *et al.* U.S. Publication No. 2003-0118592 ("Ledbetter") and McInnes *et al.* Nat Med. 3(2):198-95 (Feb. 1997) ("McInnes #2"). Applicants have canceled claims 57 and 58, so this rejection is moot as it regards these claims. The Examiner argued that McInnes #1 teaches that IL-15 mediates recruitment and activation of T cells from the peripheral blood in rheumatoid arthritis patients and that T cells in these patients have upregulated CD69 expression. The Examiner asserted that McInnes #1 did not teach the use of a depleting anti-CD69 antibody to treat rheumatoid arthritis. The Examiner further argued that Ledbetter teaches human and humanized anti-CD69 antibodies effective in the depletion of immune cells, as well as toxin conjugated antibodies. Further, the Examiner asserted that Ledbetter teaches that autoreactive T and B cells are present in rheumatoid arthritis patients and that anti-CD69 antibodies can be used to treat various autoimmune diseases and tumors. Moreover, the Examiner asserted that McInnes #2 teaches that anti-CD69 antibody blocks IL-15 activated T cell production and induction of TNFα in macrophages and monocytes. The Examiner argued that given the teachings of McInnes #1 it would have been obvious to one of ordinary skill in the art that an excellent alternative to neutralizing IL-15 would have been to treat rheumatoid arthritis by depleting CD69 expressing T-cells with an anti-CD69 antibody as taught by Ledbetter. The Examiner further argued that even if the anti-CD69 antibody would not have depleted the CD69 T-cells, the teachings of McInnes #2 show that anti-CD69 antibodies would at least prevent the T cells from producing TNFα. Applicants traverse the rejection for the reasons detailed below.

Applicants submit that claims 56, 59, 60, 67-69 and 105-108 are not obvious over McInnes #1, in light of Ledbetter and McInnes #2. First, Applicants argue that the Examiner is using an impermissible obvious to try standard. Second, Applicants show that there is no motivation to combine the teachings of McInnes #1, Ledbetter and McInnes #2. Third, Applicants assert that the methods of claims 56, 59, 60, 67-69 and 105-108 are based upon unexpected results so that one of ordinary skill in the art would not have a reasonable expectation of success in the methods of the instant claims in light of the teachings of McInnes #1, Ledbetter and McInnes #2.

Impermissible Use of the Obvious to Try Standard.

The Examiner is using an impermissible obvious to try standard in the rejection of claims 56, 59, 60, 67-69 and 105-108 over the teachings of McInnes #1, Ledbetter and McInnes #2. Obvious to try is not the standard under 35 U.S.C. § 103.[1] What is obvious to try would be to try each of numerous choices until one possibly arrived at a successful result or explore a new technology or general approach that seemed to be a promising field of experimentation.[2] The teachings of McInnes #1, Ledbetter and McInnes #2 taken together, present numerous choices to be tried, but do not lead one of ordinary skill in the art to a successful result.

McInnes #1 teaches that IL-15 can both recruit and expand CD45R0+ memory T-cells subsets in the synovial membrane which in the continued presence of IL-15 or via contact with macrophages, increase production of TNFα.[3] To remedy this, McInnes #1 teaches that IL-15 expression should be downgraded or IL-15 receptors should be targeted in order to decrease inflammation.[4] No animal study data was shown in the teachings of McInnes #1.

Ledbetter teaches binding domain immunoglobulin fusion proteins.[5] Ledbetter also teaches various cell surface antigens that may be targeted by the binding domain immunoglobulin fusion proteins.[6] One of these many proteins is CD69.[7] No specific data regarding the production of antibodies or antibody-like molecules that specifically bind to CD69 are mentioned, or antibodies or antibody-like molecules that deplete CD69+ cells. Ledbetter also mentions rheumatoid arthritis in a list of several pathologies, that may be amenable to treatment through antibodies or antibody-like molecules that specifically bind to one of many cell surface antigens.[8]

McInnes #2 teaches that peripheral blood T-cells and U937 cells that are co-cultured in the presence of IL-15 *in vitro* have decreased TNFα production when treated with an antibody to CD69.[9] There are no teachings in McInnes #2 that these antibodies deplete the cultures of $CD69^+$ cells. No animal study data was shown in the teachings of McInnes #2.

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[1] MPEP § 2145.
[2] *Id.*
[3] *See* McInnes #1 at page 77, column 1, first full paragraph.
[4] *Id.* at page 78, column 2, first full paragraph.
[5] *See* Ledbetter at the Abstract.
[6] *Id.* at paragraph 105.
[7] *Id.*
[8] *Id.* at paragraphs 137-148.
[9] *See* McInnes #2 at page 192, column 2, first full paragraph.

Applicants assert that a person having ordinary skill in the art, reviewing the combination of McInnes #1, Ledbetter, and McInnes #2 would have to try each of numerous choices until he or she possibly arrived at a successful result. McInnes #1 presents several possible therapeutic possibilities involving the use of agents that reduce IL-15 expression or IL-15 activity by acting on the IL-15 receptor. Ledbetter teaches antibody and antibody-derived molecules that bind to many cell surface antigens, including CD69, for the treatment numerous pathologies, including rheumatoid arthritis. McInnes #2 teaches the use of antibodies to CD69 to decrease the production of TNFα an *in vitro* culture of peripheral blood T-cells and U937 cells in the presence of IL-15. From these teachings, one of ordinary skill in the art would have to choose between various agents that decrease expression of IL-15, decrease the activity of IL-15, various antibodies that bind specifically to CD69 and decrease expression of TNFα, as well as depleting anti-CD69 antibodies as possible therapies for various immune conditions including rheumatoid arthritis. Further, the teachings of McInnes #1, Ledbetter and McInnes #2 have no specific evidence regarding the efficacy of depleting anti-CD69 antibodies. None of the cited references teaches a specific depleting anti-CD69 antibody, or shows any evidence of their efficacy in any context. Applicants submit that a person having ordinary skill in the art would have to try each of these numerous choices, and would have to choose the least researched choice in order arrive at the successful result of the instant claims.

No Motivation to Combine the References

Applicants assert that one of ordinary skill in the art would not have had motivation to combine the teachings of McInnes #1 with Ledbetter, nor would they have had motivation to combine the teachings of McInnes #2 and Ledbetter. One of the requirements to make a *prima facie* case for obviousness is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.[10]

One of ordinary skill in the art could not find a motivation to combine McInnes #1 with Ledbetter either in the references themselves or in knowledge generally available in the art. McInnes #1 teaches that CD69 is involved with IL-15 in the reduction of TNFα production by interacting with synovial T-cells. McInnes #1 does not teach anything regarding the treatment of

[10] MPEP § 2142

rheumatoid arthritis with depleting anti-CD69 antibodies. McInnes #1 suggests that rheumatoid arthritis may be treated through the reduction of expression or activity of IL-15. McInnes #1 does not teach or suggest that the depletion of CD69+ cells would be an effective treatment for rheumatoid arthritis. Thus, one of ordinary skill in the art would not be motivated to combine Ledbetter which teaches various depleting antibodies and related molecules for a large number of cell surface antigens, including CD69.

Likewise, one of ordinary skill in the art would not have had motivation to combine McInnes #2 and Ledbetter. McInnes #2 teaches that antibodies that bind CD69, but do not deplete CD69+ positive cells, reduce the amount of TNFα produced in *in vitro* co-cultures. There is no teaching that depleting CD69 antibodies are used to decrease TNFα production. McInnes #2 does not teach that the depletion of CD69+ cells would be an effective treatment for rheumatoid arthritis. Thus, one of ordinary skill in the art would have had motivation to combine McInnes #2 with Ledbetter which teaches various depleting antibodies and related molecules for a large number of cell surface antigens, including CD69.

Applicants further submit that the Examiner has merely asserted that a skilled artisan would have been motivated to combine the above references without identifying where in the references either explicit or implicit motivation can be found to support the rejection. Thus, the Examiner has only alleged that the references can be combined to arrive at the present invention. The mere fact that references can be combined or modified, however, does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See M.P.E.P. § 2143.01 (III). That is, a rejection based on a *prima facie* case of obviousness is improper without a motivation to combine the references. The Office Action combines facts and attempts to provide a motivation to combine the references without identifying the source of the motivation. The desirability of the combination is not suggested in any of the references cited by examiner. Accordingly, the Office Action has also failed to establish a *prima facie* case of obviousness because the cited references do not provide either explicit or implicit motivation to combine or modify the teachings of the references to arrive at the present invention.

Deputy Commissioner of Patent Operations issued a memorandum on May 3, 2007 following the Supreme Court decision on *KSR Int'l Co. v. Teleflex, Inc.* (see Exhibit A) stating the following:

> [I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

In light of the above, Applicants respectfully submit that the Office Action fails to present sufficient reason why a person of ordinary skill in the art would have combined the teachings of McInnes #1 with Ledbetter or McInnes #2 with Ledbetter.

No Reasonable Expectation of Success and Unexpected Results.

Applicants assert that a person having ordinary skill in the art reviewing the cited references would not have had a reasonable expectation of success at arriving at the methods of claims 56, 59, 60, 67-69 and 105-108, in part, because of the methods of the claims are based on unexpected results. Claims 56, 59, 60, 67-69 and 105-108 are presently being examined insofar as they encompass methods of treating rheumatoid arthritis.

One of ordinary skill in the art would not have a reasonable expectation of success regarding the methods of claims 56, 59, 60, 67-69 and 105-108 based on the teachings of McInnes #1, Ledbetter, or McInnes #2. None of McInnes #1, Ledbetter, or McInnes #2 show any *in vivo* data from animal models for arthritis. Previously, *in vivo* data had shown that constitutive expression of CD69 by T cells in transgenic mice was not associated with inflammatory conditions.[11] Also, the antigen-specific responses in transgenic mice without CD69 expression did not reveal reduced T-cell activation.[12] These *in vivo* findings contradicted *in vitro* findings showing that CD69+ T-cells were associated with inflammatory conditions.[13] One of the publications that was contradicted by *in vivo* data was McInnes #2.[14]

Contrary to previous *in vivo* findings, the instant specification shows *in vivo* treatment of collagen induced arthritis (CIA) in mice with anti-CD69 antibody.[15] CIA is a widely accepted experimental model of inflammatory joint disease and specifically rheumatoid arthritis.[16] Moreover, McInnes #1, Ledbetter, or McInnes #2 show no experimental evidence of any sort that suggests that CD69 depleting antibodies work to alleviate the symptoms of rheumatoid arthritis. As explained above, they merely invite one of ordinary skill in the art to try many

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[11] *See* Sancho *et al.* Trends in Immunology, 26(3):136-140 (2005) at page 137, column 1 first paragraph ("Exhibit B").
[12] *Id.*
[13] *Id.* at page 136, column 2, first full paragraph.
[14] *Id.* referred to as reference #15.
[15] *See* the instant specification from page 104, line 14 to page 106, line 2.
[16] *Id.* from page 30, line 30 to page 31, line 1 and Feldman *et al.* Ann Rev. Immunol. 14:397-440 (1996).

options to arrive at the claimed invention. Thus, Applicants submit that without any data on point of any kind, and previously published contradictory *in vivo* data, the teachings of McInnes #1, Ledbetter, and McInnes #2 alone or in combination provide no reasonable expectation of success to one of ordinary skill in the art.

The invention of claims 56, 59, 60, 67-69 and 105-108 is also based on unexpected results, which is evidence that the methods of these claims is non-obvious over McInnes #1, Ledbetter, and McInnes #2. The specification teaches, unexpectedly from the standpoint of one of ordinary skill in the art at the time the invention was made, that it is important that the CD69 specific antibody be a depletor of CD69+ cells, as opposed to specifically binding to CD69, while not depleting CD69+ cells. Treatment of CIA induced mice with mAb 2.2, a CD69 specific antibody that does not deplete CD69+ cells *in vivo*, exacerbated CIA in those mice.[17] Treatment of CIA induced mice with mAb 2.3, a CD69 specific antibody that depletes CD69+ cells, significantly reduced CIA.[18] Thus, the antibodies of McInnes #2 may actually exacerbate rheumatoid arthritis if they do not deplete CD69+ cells. This result was unexpected in light of McInnes #1, Ledbetter, and McInnes #2 and also other previously published *in vivo* data. Thus, Applicants submit that the methods of claims 56-60, 67-69 and 105-108 are based on unexpected properties and thus are non-obvious over McInnes #1, Ledbetter, and McInnes #2.

As explained above, Applicants submit that the Examiner's obviousness rejection is based on an improper obvious to try standard, that there is no motivation to combine McInnes #1 and Ledbetter or McInnes #2 and Ledbetter, that there is not a reasonable expectation of success from the teachings of McInnes #1, Ledbetter, and McInnes #2 to successfully arrive at the invention of claims 56, 59, 60, 67-69 and 105-108 and that the methods of claims 56, 59, 60, 67-69 and 105-108 are based on unexpected results. Thus, Applicants submit that claims 56, 59, 60, 67-69 and 105-108 are not obvious over McInnes #1 in light of Ledbetter, and McInnes #2, and respectfully requests that this rejection be withdrawn.

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[17] *Id.* at page 105, lines 3-6.
[18] *Id.* at lines 27-29 and Figure 25.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicant respectfully submits that this paper is fully responsive and that the pending claims are in condition for allowance. Such action is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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